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Abstract: Callous-unemotional traits are characterized by a lack of empathy, a disregard for others' feelings and shallow or deficient affect, such as a lack of remorse or guilt. Neuroanatomical correlates of callous-unemotional traits have been demonstrated in clinical samples (i.e., adolescents with disruptive behavior disorders). However, it is unknown whether callous-unemotional traits are associated with neuroanatomical correlates within normative populations without clinical levels of aggression or antisocial behavior. Here we investigated the relationship between callous-unemotional traits and gray matter volume using voxel-based morphometry in a large sample of typically-developing boys and girls ($n = 189$). Whole-brain multiple regression analyses controlling for site, total intracranial volume, and age were conducted in the whole sample and in boys and girls individually. Results revealed that sex and callous-unemotional traits interacted to predict gray matter volume when considering the whole sample. This interaction was driven by a significant positive correlation between callous-unemotional traits and bilateral anterior insula volume in boys, but not girls. Insula gray matter volume explained 19% of the variance in callous-unemotional traits for boys. Our results demonstrate that callous-unemotional traits are related to variations in brain structure beyond psychiatric samples. This association was observed for boys only, underlining the importance of considering sex as a factor in future research designs. Future longitudinal studies should determine whether these findings hold over childhood and adolescence, and whether the neuroanatomical correlates of callous-unemotional traits are predictive of future psychiatric vulnerability. **General scientific summary:** This study suggests that callous-unemotional traits have a neuroanatomical correlate within typically developing boys, but not girls. Bilateral anterior insula volume explains up to 19% of the variance in callous-unemotional traits in boys.

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Callous-unemotional traits and brain structure: Sex-specific effects in anterior insula of typically-developing youths

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ABSTRACT

Callous-unemotional traits are characterized by a lack of empathy, a disregard for others' feelings and shallow or deficient affect, such as a lack of remorse or guilt. Neuroanatomical correlates of callous-unemotional traits have been demonstrated in clinical samples (i.e., adolescents with disruptive behavior disorders). However, it is unknown whether callous-unemotional traits are associated with neuroanatomical correlates within normative populations without clinical levels of aggression or antisocial behavior. Here we investigated the relationship between callous-unemotional traits and gray matter volume using voxel-based morphometry in a large sample of typically-developing boys and girls ($N = 189$). Whole-brain multiple regression analyses controlling for site, total intracranial volume, and age were conducted in the whole sample and in boys and girls individually. Results revealed that sex and callous-unemotional traits interacted to predict gray matter volume when considering the whole sample. This interaction was driven by a significant positive correlation between callous-unemotional traits and bilateral anterior insula volume in boys, but not girls. Insula gray matter volume explained 19% of the variance in callous-unemotional traits for boys. Our results demonstrate that callous-unemotional traits are related to variations in brain structure beyond psychiatric samples. This association was observed for boys only, underlining the importance of considering sex as a factor in future research designs. Future longitudinal studies should determine whether these findings hold over childhood and adolescence, and whether the neuroanatomical correlates of callous-unemotional traits are predictive of future psychiatric vulnerability.

General scientific summary: This study suggests that callous-unemotional traits have a neuroanatomical correlate within typically developing boys, but not girls. Bilateral anterior insula volume explains up to 19% of the variance in callous-unemotional traits in boys.

1. Introduction

The term callous-unemotional (CU) traits refers to a pattern of behaviors including a lack of empathy, guilt or remorse, shallow or deficient affect, as well as a lack of concern about the person's actions or one's own and others' feelings (i.e., limited prosocial emotions

(American Psychiatric Association, 2013)). High levels of CU-traits are often observed in youths with severe aggression and antisocial behavior. Therefore, CU-traits have mostly been studied in children and adolescents with disruptive behavior disorders (DBDs, including oppositional defiant and conduct disorder; (Blair, 2013; Frick et al., 2014c)). Notably, children and adolescents with DBD form a very

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heterogeneous group in regard to etiology, associated behavioral symptoms, developmental trajectories, future risk for impairment, or response to treatment (Frick et al., 2014a; Frick et al., 2014c; Moffitt et al., 2008). Devising a meaningful approach to subtyping antisocial behavior has thus been of long-lasting clinical interest (Frick et al., 2014b). While various approaches have been proposed, separating individuals based on levels of CU-traits is thought to delineate a behaviorally, genetically, and neurobiologically distinct subgroup within antisocial populations (Barker et al., 2011; Bezdjian et al., 2011; Essau et al., 2006b; Frick et al., 2003; Rogers and De Brito, 2016); for reviews see (Blair, 2013; Frick et al., 2014c; Viding and McCrory, 2012). This was likewise recognized within the latest version of the DSM by an additional specifier to the diagnosis of conduct disorder termed ‘*limited prosocial emotions*’ (American Psychiatric Association, 2013). Patients qualifying for this specifier (i.e. those with elevated CU-traits) are at high risk for the development of particularly severe, persistent, and treatment-resistant forms of conduct disorder (Frick et al., 2014c).

While CU-traits have most commonly been studied in DBD populations, there is increasing evidence that CU-traits may be important in community samples without DBDs, and that CU-traits can be elevated in the absence of clinically-significant conduct problems (Fanti et al., 2013; Frick et al., 2003; Herpers et al., 2012; Kumsta et al., 2012; Rowe et al., 2010b; Viding and McCrory, 2012). CU-traits in youths without DBDs have for example been related to subclinical variations of antisocial behavior, impairments affecting peer relationships, quality of life, hyperactivity and increased risk-taking (Barker et al., 2011; Frick et al., 2003; Herpers et al., 2016; Pardini and Fite, 2010); for a review see (Viding and McCrory, 2012). CU-traits in youths with or without conduct problems are highly heritable and may carry independent diagnostic value (Barker et al., 2011; Frick et al., 2003; Herpers et al., 2017; Kumsta et al., 2012; Rowe et al., 2010a; Viding and McCrory, 2012).

To date, studies investigating the neural correlates of CU-traits have mostly focused on DBD samples. By doing so, functional neuroimaging evidence revealed that among youths with DBD, high levels of CU-traits were associated with reduced brain response during affective processing in several cortical (e.g., anterior insula, anterior cingulate cortices) and subcortical (e.g., amygdala) regions, responsible for empathic behaviors in typically developing youths (Lockwood et al., 2013; Lozier et al., 2014; Michalska et al., 2016). Prefrontal functioning in response to punishment and rewards (e.g. in the caudate and ventromedial prefrontal cortex) has in turn been shown to be increased in DBD, as opposed to a reduction in prefrontal activation typically seen in healthy children and adolescents following punishment learning ((Finger et al., 2008); for a review see (Viding and McCrory, 2017)). Additionally, studies have indicated that the functional connectivity between limbic and prefrontal brain regions, commonly impacted in DBD, was further negatively correlated with callous-unemotional traits (Marsh et al., 2008), although not all studies were able to replicate this finding (Finger et al., 2012).

In contrast to functional MRI evidence, the unique associations between CU-traits and brain structure provides mixed findings in regards to the direction and precise location of effects and further investigations in youths with and without conduct problems are needed (Blair, 2013; Cohn et al., 2016). More specifically, elevated CU-traits have been linked to both increases and decreases in gray matter volume and concentration within orbitofrontal, anterior cingulate, para-/hippocampal, and temporal cortices (Cohn et al., 2016; Cope et al., 2014; De Brito et al., 2009; Fairchild et al., 2013a; Raschle et al., 2015; Wallace et al., 2014). Amygdala alterations in correlation with CU-traits are mostly absent (Dalwani et al., 2011; Sebastian et al., 2016; Fairchild et al., 2013a); a modest association was identified by one study reporting a positive association between CU-traits and amygdala gray matter concentration in DBD youths low on CU-traits (Cohn et al., 2016). Furthermore, a meta-regression study analyzing across five voxel-based morphometry studies on DBDs published to date found that

higher CU-traits were associated with a lower reduction in GMV in the putamen and, to a lesser extent, in the right amygdala (Rogers and De Brito, 2016).

Overall, structural and functional neuroimaging findings vary with respect to the direction and precise location of the observed associations with CU-traits. This may be due to the choice of assessment tool used, the use of different data analysis packages and strategies, as well as heterogeneity (e.g. differences in demographic and clinical features/diagnoses/comorbidities) of the groups studied. For example, the mixed nature of previous findings may be related to the various measures employed to assess CU-traits. Research reports have used a range of assessments, such as the Inventory of Callous-Unemotional traits (Essau et al., 2006a), the Youth Psychopathic traits Inventory (Andershed et al., 2007), the Psychopathy Checklist: Youth Version (Forth et al., 2003), or the callous-unemotional scale of the Antisocial Process Screening Device (Frick and Hare, 2001) in order to classify participants into those with high versus low CU-traits. Variations in results to date may thus be based on differences in the measure employed, as well as differences between samples in levels of CU-traits which may reflect differences in recruitment sources (e.g., incarcerated offenders versus community samples). In order to maximize reliability of the assessments used to characterize callous-unemotional traits the American Psychiatric Association (2013) has suggested basing the assessments of limited prosocial emotions or CU-traits on multiple sources of information. However, such comprehensive measures have rarely been implemented in research studies to date.

While all evidence points towards the importance of considering sex as a variable within research designs, the majority of neuroimaging studies, particularly those on CU-traits, focus solely on males (Rogers and De Brito, 2016). This may be due to higher levels of crimes, delinquency, or aggressive and antisocial behavior being reported in boys (Loeber et al., 2013), but nevertheless limits the generalizability of the findings. Longitudinal brain imaging studies in typically developing youths have demonstrated sex-specific differences in brain maturation and cortical trajectories (Giedd and Rapoport, 2010; Lenroot et al., 2007). In fact, cortical and subcortical gray matter development has been suggested to follow an inverted U-shaped pattern with main peaks being reached one to two years earlier in females as compared to males (Lenroot et al., 2007). Likewise, epidemiologic as well as longitudinal research indicates sex-specific developmental trajectories for neuropsychiatric disorders (Giedd and Rapoport, 2010; Moffitt et al., 2008; Wilke et al., 2007).

To summarize, the majority of studies to date have only investigated the effects of variation in CU-traits in DBD populations and are thus limited by several factors: (1) it remains open whether effects previously attributed to CU-traits were actually driven by the presence of DBDs (i.e., including symptoms and behaviors not associated with CU-traits or common comorbidities such as attention deficit/hyperactivity disorder (ADHD) or anxiety), and also whether associations between CU-traits and brain structure only hold within DBD populations; (2) while epidemiologic as well as longitudinal research indicate sex-specific developmental trajectories for neuropsychiatric disorders (Giedd and Rapoport, 2010; Moffitt et al., 2008), most studies on CU-traits in DBD groups or community samples have focused solely on males, limiting the generalizability of these findings to females; and (3) the group classification employed or the measures used to assess CU-traits have varied widely across studies (Essau et al., 2006a; Kimonis et al., 2016; Viding and McCrory, 2012; Viding and McCrory, 2017). These factors, as well as the small samples that have frequently been used, possibly explain the variability in findings reported to date and the lack of replication across studies.

Therefore, the current study aimed at bridging this gap in knowledge resulting from a narrow focus on clinical populations by investigating relationships between CU-traits and brain structure in typically-developing boys and girls without DBDs using whole brain multiple regression analyses. Secondly, we aimed to test whether the

association between CU-traits and brain structure differs across boys and girls by including an interaction term for sex and callous-unemotional traits within our multiple regression analysis. Finally, we aimed to implement a comprehensive measure of CU-traits by developing a composite score based on two sources of information (self and others' rating) in order to obtain a robust index for testing for variability in brain structure related to CU-traits. Based on previous evidence in DBD and youths with conduct problems, we expected to find correlations between CU-traits and brain structure in typically-developing youths within limbic and prefrontal brain regions including amygdala, insula, and prefrontal cortex. On the basis of previous findings showing an interaction effect of sex and CU-traits in DBD (Smaragdi et al., 2017), we expected to observe distinct associations between CU-traits and brain structure in boys and girls.

2. Material and methods

2.1. Participants

For the present analyses, we included 223 typically-developing adolescents (9–18 years), who were a subset of participants from an ongoing European multi-center study investigating female conduct disorder (FemNAT-CD). All adolescents included in the present analyses were explicitly screened to be free of any psychiatric disorder, including DBDs and substance abuse. Participants underwent standardized clinical interviews and psychometric testing and took part in a neuroimaging session. On average, the two sessions took place within 8.2 ± 7.7 weeks of each other. Data were acquired at five different sites, including the Universities of Frankfurt #01 and Aachen #02 in Germany; the Psychiatric University Hospital in Basel, Switzerland #05; and the Universities of Birmingham #07 and Southampton #04, England (only site numbers will consequently be reported within the text). All participants and their caretakers provided verbal and written informed consent to take part in the study, and the study was approved by all local ethics committees.

2.2. Clinical and psychometric testing

Based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL (Kaufman et al., 1997)) diagnostic interview, we ascertained that none of the youths included in the present analyses had a current clinical diagnosis or a past history of DBDs according to DSM-5 (American Psychiatric Association, 2013). Behavioral and emotional problems within the past 6 months were assessed using the Child Behavior Checklist (CBCL: 120 items, answered using a three-point Likert scale (Achenbach, 1991)). Since we explicitly aimed to study CU-traits in non-aggressive individuals, participants scoring $T \geq 70$ on the aggression and/or the delinquency subscales of the CBCL were excluded from our analyses (see Fig. S1). However, to be even stricter, we also re-ran our analysis with a more stringent criterion (all individuals with a T-score ≤ 65 on either the delinquency or aggression subscale of the CBCL) and did not observe a change in our main findings. IQ was assessed using the short-form of the Wechsler Abbreviated Scale of Intelligence (WASI (Wechsler, 1999)) at English speaking sites (#04, #07) or the German version of the Wechsler Intelligence Scale for Children < 17 years (WISC-IV, (Petermann and Petermann, 2011)) and the Wechsler Adult Intelligence Scale (WAIS-III, (Wechsler, 1997)) for sites #01, #02 and #05. All t- and standard scores were first z-transformed prior to any analysis. Empathy scores were measured using the parental report of the Griffith Empathy Measure (GEM: 23 items, answered using a nine-point Likert scale; (Dadds et al., 2008)).

CU-traits were measured using parent ratings on the Inventory of Callous-Unemotional traits (ICU (Essau et al., 2006a)) and self-ratings on the Youth Psychopathic traits Inventory (YPI (Andershed et al., 2007)). The ICU (a 24-item parental report) has three subscales:

callousness, uncaring, and unemotional, as well as a total score. Reliability values for the ICU lie within the range of acceptable to good (Cronbach alpha range: 0.77–0.89) (Essau et al., 2006a). The YPI (a 50-item self-report) comprises ten subscales, which generate the following three dimensions: callous-unemotional, grandiose-manipulative and impulsive-irresponsible (Andershed et al., 2007). Previous reliability scores of the YPI dimensions range from moderate to good (Cronbach's alphas of 0.36–0.71). While there is a validated short form of the YPI available for children aged 9–12 years, we used the original YPI for all ages because these versions differ only minimally and only the original YPI is available in all languages represented here (Andershed et al., 2007; van Baardewijk et al., 2008). A Cronbach's alpha for the ICU total score of 0.79 (confidence interval: 0.74–0.83) and a Cronbach's alpha for the YPI callous-unemotional dimension of 0.79 (confidence interval: 0.74–0.83) was found in the present sample. We based CU-traits on multiple sources of information in order to maximize reliability, in line with suggestions by the American Psychiatric Association (2013). However, it is worth noting that we computed a composite score based on parent and child-ratings from two different instruments. Specifically, mean scores representing the YPI callous-unemotional dimension and the ICU total were z-transformed and a new composite score for 'CU-traits' was built by calculating the mean of the two resulting z-scores. The usefulness of this new composite score was verified by: (1) Running a reliability analysis including all respective items (Cronbach's alpha of 0.83; CI: 0.79–0.87); (2) Investigating correlations between ICU total, YPI callous-unemotional scale and composite CU-traits score and brain structure in separate analyses; and (3) Testing for significant differences between the Cronbach alphas for the old and new CU-traits measures (see Supplement 2). The new composite score showed significantly higher internal reliability as compared to the ICU total score or the YPI callous-unemotional dimension. The composite scores were normally distributed and showed sufficient variance to justify a dimensional approach (Supplement 3).

ICU and YPI scores, as well as the new composite scores are presented in Table 1. Overall, scores observed in the present sample are comparable to those reported in community samples or control groups in previous neuroimaging studies (Essau et al., 2006a; Fairchild et al., 2013a). Boys scored significantly higher than girls on several subscales of the YPI, ICU or the composite measure as analyzed using two-sample t-tests as implemented in SPSSv23 (IBM Corp., Armonk, N.Y., USA).

2.3. Structural image acquisition

Participants completed between one and three functional neuroimaging tasks and/or diffusion tensor imaging scans in addition to structural T1-weighted magnetization prepared rapid gradient echo imaging (MPRAGE) on Siemens 3 T (#01/#04: Trio; #02/#05: Prisma) or Philips 3T (#07: Achieva) scanners. Each site underwent a site qualification procedure prior to starting data collection in which a radiological (ACR) phantom and healthy volunteers were scanned using multiple sequences (Chen et al., 2004). The resulting data were reviewed by an MR physicist, and scanning parameters were adjusted until the protocols were comparable (see acquisition parameters in Table S4).

2.4. Voxel-based morphometry (VBM) analysis and statistics

We utilized the computational anatomy toolbox (CAT12; <http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>) as implemented in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) and executed in MATLAB (Mathworks, Natick, MA). To account for the young age of the participants, we employed an adapted VBM-workflow that implemented customized tissue probability maps (TPM) as created through the template-o-matic toolbox (TOM8; <https://irc.cchmc.org/software/tom/downloads.php>) and a customized DARTEL template based on the gray and white matter tissue segments of all participants. Analysis steps

Table 1
Group characteristics – psychometrics and clinical testing.

| | Girls (N = 108) | Boys (N = 81) | p-value | |
|----------------------------|-----------------|-----------------|--------------|-----|
| | Mean (± SD) | Mean (± SD) | Two-sample T | |
| Age in years | 13.9 (± 2.9) | 13.2 (± 2.5) | 0.850 | |
| IQ | 105.5 (± 10.4) | 106.6 (± 11.4) | 0.486 | |
| Psychopathic traits (YPI) | | | | |
| Psychopathy (YPI total) | 87.6 (± 17.0) | 96.1 (± 18.0) | 0.001 | *** |
| Grandiose, manipulative | 32.0 (± 8.4) | 35.1 (± 9.4) | 0.020 | * |
| Callous, unemotional | 25.3 (± 5.7) | 29.4 (± 5.8) | < 0.001 | *** |
| Impulsive, irresponsible | 30.2 (± 6.1) | 31.7 (± 6.5) | 0.115 | |
| CU-Traits (ICU) | | | | |
| ICU total | 15.3 (± 7.2) | 18.3 (± 7.5) | 0.006 | ** |
| Uncaring | 7.2 (± 4.1) | 8.6 (± 4.2) | 0.024 | * |
| Unemotional | 4.2 (± 2.5) | 5.1 (± 2.6) | 0.019 | * |
| Callousness | 3.9 (± 3.0) | 4.6 (± 2.5) | 0.080 | |
| Callous-unemotional traits | | | | |
| Composite score | − 0.2 (± 0.8) | 0.3 (± 0.7) | 0.001 | *** |
| CBCL | | | | |
| Anxiety/depression | 55.5 (± 6.2) | 54.1 (± 5.9) | 0.121 | |
| Attention problems | 53.4 (± 4.9) | 53.1 (± 5.0) | 0.677 | |
| Delinquency | 52.3 (± 5.1) | 52.3 (± 3.9) | 0.999 | |
| Aggression | 52.7 (± 4.4) | 51.7 (± 5.4) | 0.160 | |
| Internal problems | 49.7 (± 10.0) | 49.7 (± 10.0) | 0.868 | |
| External problems | 47.7 (± 8.5) | 46.6 (± 8.1) | 0.385 | |
| Total problems | 48.4 (± 9.6) | 47.4 (± 9.3) | 0.472 | |

IQ = intelligence quotient (Z-scores); YPI = youth psychopathic traits inventory (mean scores); ICU = inventory of callous-unemotional traits (mean scores); CBCL = child behavior checklist (T-scores).

*** Significant at $p \leq 0.001$.

** Significant at $p \leq 0.01$.

* Significant at $p \leq 0.05$.

included:

2.4.1. Quality control

Prior to preprocessing, all images passed a first visual quality check targeting motion, gross anatomical artifacts and assuring whole-brain coverage. After preprocessing, additional information about data-quality (resolution, noise and bias) was provided by CAT12. We assured that all data had a weighted average quality of B or higher, representing very good image quality (<http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>). Finally, prior to statistical analysis we conducted another quality assessment by displaying the sample homogeneity using standard deviations through the CAT12 toolbox. Of the 223 scans reviewed, 14 had to be excluded due to motion artifacts and 2 individuals were excluded from the analysis due to significantly enlarged ventricles, resulting in $N = 207$.

2.4.2. Customized tissue probability maps (TPMs) and Dartel template creation

Customized TPMs were created using an average approach within TOM8 including vectors for age and sex, representing each of the 207 participants with useable T1 data based on the previous step (Wilke et al., 2008). All images were segmented into gray matter, white matter and cerebrospinal fluid (whereas customized TPMs were inputted during affine registration) and the affine registered tissue segments were used to construct a customized DARTel template representing the entire study sample. Finally, the template was normalized to MNI and registered to MNI (ICBM) space.

2.4.3. Preprocessing and calculation of total intracranial volume (TIV)

Preprocessing was achieved through segmentation of all data using

the custom template/TPMs and a Gaussian smoothing kernel of 8 mm. Total intracranial volume (TIV) was calculated for each participant through CAT12. Since we were interested in group-based variations in the absolute tissue (gray matter volume), TIV was consequently incorporated in the statistical analysis to account for differences in brain size.

2.4.4. Statistical analysis

Prior to analysis, we excluded two participants with high scores on the aggression and delinquency subscales of the CBCL (≥ 70 ; see methods section for further explanation). Additionally, YPI or ICU subscale data were missing for 16 individuals which were consequently excluded from subsequent analysis. The total N entering statistical analysis was therefore 189 participants (108 female, 81 male). The DARTel-normalized gray matter volumes entered multiple regression models linking CU-traits with brain structure. An interaction term for CU-traits and sex was computed by multiplying the z-standardized CU-traits with the dichotomous sex variable. The interaction term between CU-traits and sex was then entered as a covariate within the multiple regression model. Scanning site, age and TIV were added as covariates of no interest and statistics were conducted for gray matter volume only. *F*-tests were used to assess the main effect of CU-traits and the interaction between CU-traits and sex. Multiple regression analyses in each sex individually were subsequently used to further specify the direction of the results observed. The implemented *t*-tests were masked for the regions identified through the main analysis. Whole brain results are reported with a $p < 0.05$, family-wise error (FWE) correction, using the Threshold-Free Cluster Enhancement technique (TFCE according to (Smith and Nichols, 2009) with 10,000 permutations).

3. Results

3.1. Voxel-based morphometry results

Total intracranial volume was calculated for use as a covariate within the multiple regression analysis of absolute brain volume (TIV: [girls/boys] = [1414.4 ± 112.9 / 1580.6 ± 126.2]), white (WM: [girls/boys] = [470.3 ± 49.8 / 529.3 ± 48.5]) and gray matter volume (GM: [girls/boys] = [702.3 ± 57.8 / 790.1 ± 71.3]). In line with previous findings (e.g. (Giedd and Rapoport, 2010)), girls and boys significantly differed in total intracranial volume (for TIV, GM and WM; all $p < 0.001$).

3.1.1. Multiple regression analyses

Across all girls and boys ($N = 189$), there were no significant positive or negative correlations between CU-traits and gray matter volume. However, there was a significant interaction effect for sex and CU-traits in bilateral clusters encompassing anterior insula, claustrum and inferior frontal gyrus ($p < 0.05$; FWE TFCE corrected; see Fig. 1). In order to assess the direction of this interaction effect further, we performed follow-up analyses in boys and girls individually, with a restricted analysis mask for left and right anterior insula based on the significant clusters identified through the interaction effects across the whole sample.

3.1.2. Multiple regression analysis in boys

For boys, CU-traits were significantly positively correlated with gray matter volume of the previously identified bilateral anterior insular cortices ($p < 0.05$; FWE TFCE corrected; see Table 2 and Fig. 1).

3.1.3. Multiple regression analysis in girls

Within females, there were no significant positive or negative correlations between CU-traits and gray matter volume when restricting the multiple regression model to the bilateral anterior insula as identified by our interaction analysis.

The robustness of the here observed significant interaction effect

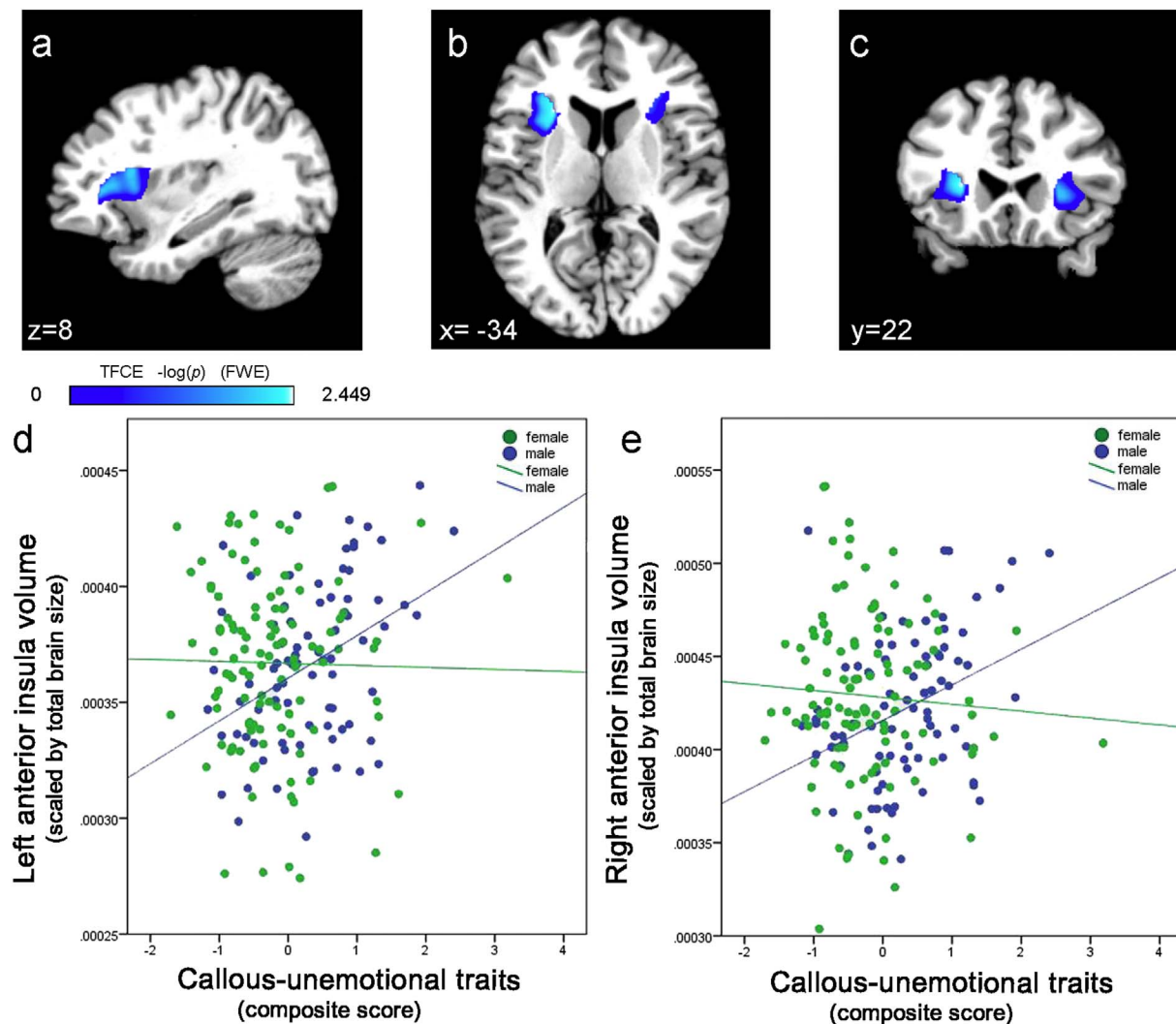


Fig. 1. Statistical parametric maps showing a significant positive correlation between callous-unemotional traits and bilateral anterior insula volume in boys (in blue; displayed a = axial, b = sagittal, c = coronal views using the Multi-image Analysis GUI, available at <http://ric.uthscsa.edu/mango/mango.html>; $p < 0.05$; FWE TFCE corrected) and correlations between callous-unemotional traits and gray matter volume in independent left (d) and right (e) anterior insula regions of interest for boys (blue) and girls (green).

between CU-traits and sex within bilateral anterior insula across the whole group was further tested by accounting for aggressive behavior. Our results remained significant when a covariate based on scores from the CBCL aggression subscale were added into our multiple regression analysis. Additionally, we assessed a sex-matched group (81:81), excluding participants from center #5 (only female participants). The analysis resulted in a similar outcome of an interaction effect in bilateral anterior insula at an uncorrected $p < 0.001$ (only left anterior insula remained significant for this group at $p < 0.05$; FWE TFCE corrected).

3.1.4. Post-hoc region of interest analyses

Post-hoc region of interest and partial correlation analyses were conducted using the marsbar toolbox (<http://marsbar.sourceforge.net/>) to extract gray matter volume and SPSS v-23 to run statistical analyses. Bilateral anterior insula regions of interest were created using 5 mm-radius spheres around the MNI coordinates ($x = -32$, $y = 22$, $z = -2$) and ($x = 36$, $y = 22$, $z = -6$) as derived from a coordinate-based meta-analysis (Rottschy et al., 2012). The average mean gray matter volume indices for these regions of interest were extracted and scaled by each individual's TIV, in order to avoid multicollinearity and adjust for unmodulated scores. Resulting values were used to address three post-hoc aims, namely: (1) Investigate the specific CU-traits-

bilateral insula associations for boys and girls separately; (2) Investigate the amount of variance in CU-traits accounted for by variations in bilateral insula volume in boys, as was done previously in adult studies (Cope et al., 2014; Ermer et al., 2013); and (3) Investigate potential age effects on the bilateral insula findings in boys. Post-hoc results revealed significant positive correlations between left and right insula volumes and CU-traits in boys (Fig. 1d–e). Although no significant correlations between CU-traits and anterior insula volumes were observed in our whole brain analysis in girls, additional post-hoc region of interest-based analysis were conducted for anatomically defined bilateral anterior insula in order to further evaluate and confirm this null relationship. These findings indicated a trend towards an opposite (negative) association between insular volume and CU-traits in girls, which did not reach formal levels of statistical significance. Additionally, we statistically examined whether the regressions (correlation between CU-traits and left and right anterior insula for boys and girls) significantly differed from each other by calculating Fisher's z (Diedenhofen and Musch, 2015). For both left ($z = -3.54$, $p = 0.0004$) and right ($z = -4.38$, $p < 0.0001$) anterior insula, the slopes significantly differed across boys and girls. Secondly, the scaled mean gray matter bilateral insula volumes were entered as predictors into a multiple regression model with CU-traits scores as the dependent variable. The resulting model for boys, excluding the influence of the covariates,

Table 2

Montreal Neurological Institute neuroanatomical coordinates, cluster size and *p*-scores representing the peak coordinates for significant interaction effects in all youths and positive associations between callous-unemotional traits and gray matter volume in typically-developing boys, but not girls ($p < 0.05$; FWE TFCE corrected).

| | k | MNI coordinates | | | <i>p</i> (FWE) | |
|---|----------|-----------------|------|----|-------------------|---------|
| | | x | y | z | | |
| Interaction: callous-unemotional traits × sex | | | | | | |
| L insula, claustrum, inferior frontal gyrus | 644 | − 26 | 22 | 8 | 0.003 | |
| R insula, claustrum, inferior frontal gyrus | 161 | 28 | 21 | 2 | 0.001 | |
| | | | | | | |
| | k | MNI coordinates | | | <i>p</i> (FWE) | |
| Direction | | x | y | z | | |
| Masked post-hoc analysis in boys (<i>N</i> = 81) | | | | | | |
| L insula, claustrum, inferior frontal gyrus | positive | 644 | − 28 | 22 | 3 | < 0.001 |
| R insula, claustrum, inferior frontal gyrus | positive | 161 | 30 | 21 | 0 | < 0.001 |
| Masked post-hoc analysis in females (<i>N</i> = 108) | | | | | | |
| ns | – | – | – | – | – | |

k = cluster size; R = right; L = left; ns = no significance.

reached significance ($p < 0.001$) and indicated that variations in bilateral anterior volume explained 19.4% of the variance in CU-traits. Finally, within our multiple regression model, we showed that age did not explain any additional variance in bilateral insula volume findings in boys (significant *F*-change = 0.148). This effect was further investigated using an *F*-test within the multiple regression model in SPM, plotting positive and/or negative effects of age on bilateral anterior insula volume shown to be associated with CU-traits in boys. No significant effects of age on associations between CU-traits and anterior insula volume were observed.

4. Discussion

In a sample of typically-developing community boys and girls, we show for the first time that callous-unemotional (CU) traits were correlated with the volume of the anterior insula, independent of disruptive behavior disorders (DBDs). This association was sex-specific, with CU-traits showing a significant positive correlation with bilateral anterior insula volume in boys alone. Overall, anterior insula volume accounted for 19.1% of the variance in CU-traits among boys; this is comparable to the informative value of structural associations in adult psychopathy (Cope et al., 2014; Ermer et al., 2013). The present study generated a composite CU-trait score based on multiple sources of information (i.e. self and parent-report). In line with previous authors before and according to psychometric evaluations (American Psychiatric Association, 2013; Essau et al., 2006a), we consider this a potential strength. However, we acknowledge that comparability with previous findings may be impacted as a result of using a newly generated measure of CU-traits.

4.1. Callous-unemotional traits and brain structure in boys

Our analysis identified the bilateral anterior insula as a structural correlate of CU-traits in typically-developing boys, but not girls. Previous studies point towards a functionally plausible parcellation of the insula into at least three distinct sub-regions, subserving chemosensory and socioemotional processing (ventro-anterior), higher

cognitive processing (dorso-anterior) and pain or sensorimotor processing (posterior) (Chang et al., 2013). The correlation between CU-traits and brain structure observed here was strongest in bilateral anterior insula extending to the inferior frontal gyrus. The anterior insula has consistently been linked to emotion processing and empathy, and is activated in fMRI studies tapping these domains; it has additionally been associated with cognitive control mechanisms (Fan et al., 2011; Phan et al., 2002; Sundermann and Pfeleiderer, 2012).

Past research has revealed structural and functional alterations in the anterior insula of individuals with DBDs (Blair, 2013; Cohn et al., 2013; Fahim et al., 2011; Raschle et al., 2015; Rogers and De Brito, 2016; Sterzer et al., 2007). Thereby, functional neuroimaging has linked atypical empathic responding, emotional learning and decision-making to the anterior insula (Blair, 2013; Lockwood et al., 2013; Michalska et al., 2016; White et al., 2012; White et al., 2016). In DBDs high levels of CU-traits are further positively correlated with the amount neural reduction in limbic areas during affective processing and are considered reflective of a diminished empathy for pain (Lockwood et al., 2013; Michalska et al., 2016; Viding and McCrory, 2017). However, atypical neural correlates in DBD during reinforcement learning which also implicate insular cortex, have not identified the same (or any) further association based on CU-traits (White et al., 2012; White et al., 2016). This may indicate that in DBD impaired insula functioning during affective processing (e.g., (Lockwood et al., 2013; Michalska et al., 2016)), but not reinforcement learning is further associated with variations in CU-traits (White et al., 2012; White et al., 2016); for a review see (Viding and McCrory, 2017). The association between CU-traits and brain anatomy is still matter of investigations. For example one study reported increases in insular cortex gray matter volume in DBD youths with high CU-traits (De Brito et al., 2009), others found a negative correlation between anterior insula volume or concentration and CU-traits in at-risk youths (Cohn et al., 2013) or DBD girls (Fairchild et al., 2013a), but the association in the latter study remained non-significant after correcting for CD symptoms (Fairchild et al., 2013a).

Differences in reports of increased or decreased gray matter in anterior insula in community samples of boys, or boys as compared to girls, with elevated CU-traits may reflect maturational effects (i.e. delayed maturation of this region in males). Reports of an inverted U-shaped development for the insular cortex and differences in rates of cortical maturation between girls and boys of about 1–3 years support this hypothesis (Giedd and Rapoport, 2010). However, comparability to studies in DBD is complicated since the developmental trajectories between groups of children with and without psychiatric diagnosis may likewise differ (Giedd and Rapoport, 2010). Our findings of a positive association between CU-traits and brain structure in boys diverge from studies in DBD that have suggested a negative association between CU-traits and insula volume (i.e. see meta-analysis by (Rogers and De Brito, 2016)) or aggression scores and insula volume across both CD and control participants (Sterzer et al., 2007). This could suggest that the association between CU-traits and brain structure follows a different trajectory in typically-developing youths as compared to those with DBDs. However, differences may also be based on group selection (number of participants, clinical criteria, age, sex-ratio) or construct employed (e.g. measuring CU-traits versus empathy more specifically).

4.2. CU-traits and brain structure in girls: Sex differences?

We found no significant relationships between CU-traits and gray matter volume in a large sample of girls (N = 108). Sex differences in insula structure and function, as well as sex differences in gray matter volume developmental trajectories, as mentioned above, may provide an explanation for this finding (Giedd and Rapoport, 2010; Lenroot et al., 2007). Furthermore, studies investigating the impact of CU-traits in DBD populations have almost exclusively focused on males, and therefore have not allowed a validation of the constructs employed in

females (Rogstad and Rogers, 2008). It is a matter of ongoing debate whether differences in CU-traits between boys and girls represent true sex differences or whether the instruments, which have predominantly been developed in male samples, do not apply as well to females (Rogstad and Rogers, 2008). We suggest that the fact that did not observe a significant association between CU traits and gray matter volume does not result from measurement issues since the variance in the separate CU-traits subscores are similar within each sex. While the consideration of sex-differences in brain imaging studies is a controversial issue, bearing in mind the implications of incorrect conclusions (Cosgrove et al., 2007), future studies should focus on including and comparing both sexes in order to enhance our understanding of sex differences and apply this information to the study of neurodevelopmental and psychiatric disorders (i.e., DBDs), even if these are more prevalent in males. Ultimately, large-scale longitudinal studies are needed in order to answer the question whether the neuroanatomical differences observed here are of a developmental (e.g. through a time-specific shift in the cortical growth curve of boys and girls) or a fundamental nature (e.g. present across development).

4.3. Study limitations

This study had several limitations that should be considered when interpreting the results. First, while multicenter neuroimaging studies do offer considerable advantages in terms of increased sensitivity by including a higher number of participants, they also introduce challenges of inter-site variability which may introduce additional noise and potential systematic errors unless this factor is carefully controlled for (Chen et al., 2014; Takao et al., 2014). For example, Takao et al. (2014) demonstrate the importance of balanced case and control ratios within structural multicenter neuroimaging analyses by discussing the example of sex differences (Takao et al., 2014). We cannot fully exclude the possibility that remaining site differences and/or variations in the distribution of CU-traits across sexes have influenced our findings. Furthermore, previous evidence suggests that volumetric brain alterations derive from changes in both cortical thickness and surface area (Panizzon et al., 2009). Investigating gray matter volume indices in relation to CU-traits cannot indicate which factor(s) has or have contributed to the results. For example, in a study comparing youth with conduct disorder and controls, cortical thickness and folding deficits were demonstrated to localize to different (posterior versus anterior) brain structures (Hyatt et al., 2012). However, an advantage of using a voxel-based morphometry approach is to increase the comparability with past studies. It is also notable that while we assured that the identified insula findings in boys were not influenced by age within the range included, future studies will need to assess more complex issues related to development, which could not be answered using the present sample (e.g. stability of the observed associations across age). Finally, while we have ensured that CU-traits are normally distributed within our sample, thereby allowing us to adopt a dimensional approach, the scores reported here are representative of a community sample and substantially lower than mean CU-traits scores reported in youths with conduct problems (e.g. Fairchild et al., 2013a; Marsh et al., 2008). While we here demonstrate sex-specific effects of CU traits in typically-developing boys and girls, we note that any comparisons between the present study and the existing literature on DBDs are limited by not including boys and girls with DBDs and varying levels of callous-unemotional traits.

4.4. CU-traits as a dimensional construct

We here demonstrate the usefulness of CU-traits as a potential neurobiological specifier in adolescent boys beyond clinical populations. More specifically, CU-traits showed associations with brain structure in typically-developing boys, without diagnosable levels of antisocial behavior. Our findings thus support a dimensional approach

to understanding mental health, as implemented within the Research Domain Criteria framework (Blair, 2015). Moving away from categorical classifications, variations in traits are used to describe individual phenotypes. Frameworks assessing such traits must be able to differentiate not only across the clinical spectrum, but also within samples of typically-developing youths (Garvey et al., 2016). While our findings of sex-specific positive effects between insula gray matter volume and CU-traits in typically-developing boys but not girls are somewhat surprising given previous opposite findings in DBD boys or mixed gender samples (Lockwood et al., 2013; Lozier et al., 2014; Marsh et al., 2008) or positive findings in DBD girls (Fairchild et al., 2013a), it is mentionable that the direction of findings across prior studies varies (i.e. increases versus decreases of neural functioning or gray matter volume; e.g. (De Brito et al., 2009)). This may indicate a different relationship between CU-traits and brain structures in typically-developing youths relative to findings obtained in DBD youth. Interestingly, a recent voxel-based morphometry study in at-risk adolescents demonstrated a positive correlation between CU-traits and insular cortex volume in individuals with low, but not high, levels of CD symptoms (Cohn et al., 2016). The study may be interpreted in line with the present analysis in typically developing youths who were deliberately selected to be low in or free of conduct problems and DBD symptoms. However, it is to mention that in the study by Cohn et al. (2016) even youths low on CU-traits were childhood arrestees before the age of 12.

Another point to consider is that while CU-traits designate a risk factor for the development of serious conduct problems (e.g., (Frick et al., 2014a)), the stability of these traits over time is less clear. More specifically, longitudinal research demonstrates that while children high in psychopathic traits at around age 13 have a higher chance to display high psychopathy scores in adulthood, only 9% of the variance in adulthood was actually explained by scores at age 13 (Lynam et al., 2007). Thus, while high levels of CU-traits may be a risk factor for negative outcomes in some children, they may not remain high over time, and a significant proportion of those with elevated scores will not develop clinically relevant difficulties, such as conduct disorder. In the present analysis, CU-traits were positively associated with bilateral anterior insula volume in boys. While this may be indicative of a heightened risk to develop conduct problems later in life, it is notable that none of the boys had elevated levels of conduct problems or DBD diagnoses at the time of assessment. It is also likely that many of them will not go on to show such difficulties.

Assuming that the present structural variations relate to insula functioning, our findings may be interpreted as consistent with theories implicating atypical insula functioning in populations with CU-traits or antisocial features. However, it remains to be investigated whether variations in CU-traits and insula structure may serve as a potential risk factor for the development of future clinical, social, and psychological problems. However, alterations in brain structure alone may only be a latent or probabilistic risk factor, which, without an environmental trigger, may never manifest as psychopathology (see also (Fairchild et al., 2013b)).

Future studies will need to examine the relationship between CU-traits and brain structure, not only in typically-developing individuals, but across the whole spectrum, which includes at-risk children or those with DBDs. By doing so, large-scale neuroimaging studies should investigate whether the structural variations accompanying CU-traits in boys, as identified here, are individually, or in combination with further environmental variables, predictive of future psychiatric illness or psychosocial maladjustment (Viding and McCrory, 2012).

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Conflict of interest statement

CMF has served as a consultant for Desitin and Roche. She receives royalties for books on ADHD, ASD and MDD.

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